

Review Article

Ocular Toxicity of Iron Chelator Drugs among Thalassemia Patients; a Review

Nader Nassiri ¹, MD; Mozhgan Hashemieh ^{*2}, MD

1. Department of Ophthalmology, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2. Department of Pediatric Hematology Oncology, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

***Corresponding Author:** Mozhgan Hashemieh

E-mail: mozh_hash@yahoo.com

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Abstract

Transfusion dependent thalassemia is a hematological condition characterized by imbalance in synthesis of alpha and beta subunits of hemoglobin. The consequence of regular and repeated transfusions is iron deposition in different organs. In order to survive, these patients need iron chelator drugs. The oldest drug of this group is desferrioxamine which is administered subcutaneously or intravenously. Nowadays, oral iron chelator drugs, including deferiprone and deferasirox are in more widespread use since they are more convenient. In this review the ocular toxicity of these chelator drugs is discussed.

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Introduction

Thalassemia syndromes are a type of hereditary hemolytic anemia characterized by reduction or absence of β -chains synthesis¹. Iran is located on thalassemia belt with an overage carrier rate of 4 %^{2,3}. It is estimated that each year 60,000 to 70,000 beta thalassemia cases are born most of them in the Mediterranean area, Middle East, Far East and East Asia⁴. The main part of management for these patients is regular transfusions. The consequence of these repeated transfusions is iron accumulation in vital organs, such as heart, liver, endocrine glands and kidneys⁵. Therefore to improve the survival of thalassemia patients, iron chelator drugs are used⁶. Without adequate transfusion and chelation, the life expectancy among thalassemia patients is much lower than normal population⁷.

Thalassemia can affect eyes⁸. Ocular complications of thalassemia syndromes can be due to different factors such as chronic hypoxia, bone marrow expansion, iron overload and deferoxamine toxicity⁹. Three iron chelators have been approved for iron chelation in thalassemia: deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX)¹⁰. DFO was the first generation of iron chelators administered intravenously or subcutaneously over duration of 8-10 hours per day; 5-7 days week¹¹. The most common side effects of DFO are local irritation, redness and itching at the site of injection, skeletal changes, ocular abnormalities and auditory disturbances such as hearing loss and tinnitus¹². The life-threatening side effect of oral chelator drug DFP is agranulocytosis, which can be fatal¹³. DFX is another oral iron chelator which is usually used once-daily. Gastrointestinal disturbances, fever, headache, cough, mild to moderate elevation of the creatinine level,

elevation of liver enzymes, hearing loss and ocular disturbances including cataracts and retinal disorders have been reported as the side effects of this drug¹⁴. In this review the ocular toxicity of these chelator drugs will be discussed.

Ocular side effects of deferoxamine

Ocular findings in beta thalassemia may be caused by the disease itself, iron overload or chelator drugs⁹. Baath et al., have reported an incidence of 1.2 % for ophthalmologic complications of DFO, but their low sample size of just 84 patients receiving regular DFO treatment for transfusional hemochromatosis related to long-term hypertransfusion makes this percentage somehow unreliable¹⁵. In other studies this incidence has been reported to be between 1 % to 9 %¹².

There seems to be no clear relationship between drug dosage and development of DFO retinopathy, but intravenous DFO presents a greater risk of retinal toxicity compared to subcutaneous and intramuscular forms of DFO¹⁵. Other probable risk factors include blood-retinal barrier breakdown among diabetic patients, rheumatoid arthritis, renal failure and metabolic encephalopathy¹². The mechanism of DFO ocular toxicity is not well understood but the ocular side effects of DFO were first suggested to be caused by chelation of metals, which are essential for normal retinal function, in particular copper, by DFO¹⁶. A direct effect not secondary to trace element depletion, caused by cell death due to activation of p38 mitogen activated protein kinases, has also been suggested¹².

The probable ocular side effects of DFO include decreased visual acuity or acute visual loss, color vision abnormalities, impaired visual field, night blindness, angioid streaks, retrobulbar optic neuritis, bull's eye

maculopathy, vitelliform maculopathy and macular or peripheral pigmentary degeneration^{9,12,16-19}.

There is no gold standard for identification of the ocular toxicity caused by DFO prior to its development¹². Patients might show changes in their response to visual evoked potentials testing after DFO administration²⁰. However in majority of cases, investigations such as electroretinography and fluorescein angiography are carried out only when an abnormality is found in clinical history or physical examination of the eye¹⁵. Currently, there are no approved guidelines for the follow-up and no agreed upon treatment for DFO ocular toxicity other than drug discontinuation or dose reduction¹². A maximum dose of 50 mg/kg of body weight and tapering the dose as the hepatic iron concentration approaches normal levels is suggested to minimize the ocular toxicity¹².

Ocular side effects of deferiprone and deferasirox

Nowadays because of inconvenient use of DFO, the majority of thalassemia patients consume oral iron chelator agents like DFP, which also have fewer systemic side effects²¹. DFP provides effective retinal iron chelation because of its ability to cross the blood-retinal barrier without retinal toxicity^{18,22}. Posterior subcapsular opacity and retinal pigment epithelium degeneration due to deferiprone use have been reported^{18,23-27}. Deferasirox is another oral iron chelator with no retinal penetration²⁸. Lens opacities, reversible retinopathy, and toxic maculopathy have been reported in patients using this drug²⁹⁻³³. It should be noted that since DFP and DFX are comparatively new drugs compared to DFO, our body of knowledge about their ocular toxicity is very limited, consisting of mostly

anecdotal case reports.

Discussion

Eye practitioners need to consider ocular complications caused by thalassemia itself, transfusional iron overload, or iron chelators when examining a thalassemia patient and close follow-up using various imaging modalities may help to lessen ocular damage among these patients¹⁸. It should be noted that chelator drugs are the cause of some ocular complications among thalassemic patients, but most of the ocular complications in beta-thalassemia patients are caused by the disease itself⁹.

Regular ophthalmic screening should be carried out for thalassemic patients receiving chelator drugs because early detection of eye toxicity caused by these drugs may lead to optimization of the drug dosage and prevent the long-term visual consequences¹⁵. It has been suggested that ophthalmic screening should be performed at three months intervals along with maintaining therapeutic levels of desferrioxamine under 0.025 microgram/l of blood to help in prevention and reversal of ocular toxicity among thalassemic patients³⁴.

Taher et al. have reported that the type of iron chelating agent used had no influence on the decrease in visual acuity²³. There are conflicting reports about the reversibility of chelator drugs ocular toxicity. Retinal changes and visual deficits might recover after cessation of the medication, but some authors have reported permanent visual deterioration or progression of ocular complications, even after drug discontinuation^{15,35}. Rahi et al.,³⁶ reported a case who presented with both central scotoma and constriction of the peripheral field in each eye, which resolved after withdrawal of high-dose therapy. Also Marciani et al.,³⁷ in their study of high-dose

DFO therapy in patients with iron overload reported reversible visual impairment without significant changes in brain electrical activity. In contrast Bene et al.,³⁸ have reported a case of irreversible visual loss after deferoxamine usage. Similarly Simon et al.,³⁴ have reported a 29-year-old patient receiving repeated blood transfusions for β thalassemia since childhood developing blindness and peripheral visual field loss shortly after commencing high-dose intravenous desferrioxamine. In their case the recovery was partial following cessation of desferrioxamine³⁴.

In brief although the ocular toxicity of iron chelator drugs among thalassemia patients

is relatively rare it might cause devastating consequences for the patient. The proper management of these patients includes regular eye exams, early detection of toxicity and discontinuation of the causative drug, which needs close coordination between the eye specialists and hematologists managing these patients.

Conclusion

Iron chelator drugs might cause various ocular side effects. Regular ophthalmic screening in all thalassemia patients receiving iron chelator drugs is recommended to avoid delayed diagnosis and irreversible damage to patients' eyes.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present study.